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CATATONIC STUPOR SECONDARY TO GAMMA-HYDROXY-BUTYRIC ACID (GHB)-DEPENDENCE AND -WITHDRAWAL SYNDROME

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INTRODUCTION

GHB has been formerly used as an anesthetic and developed into a popular psychoactive drug. GBL is primarily used as a solvent in the pharmaceutical industry, is a precursor of and following hepatic hydrolysis by the 1-4 Lactonase converted to GHB. The plasma half-life of GBL is short, can be detected only less than one minute and the main active metabolite is GHB (Scheep et al. 2012).

The pharmacokinetics of GHB indicate a short action. The time to peak serum levels ranges from 36-57 minutes and the elimination half-life between 30-52 minutes. Addiction occurs when prolonged, repeated GHB use disrupts the balance of brain transmitters and circuits controlling reward, memory and cognition leading to compulsive use. The duration of clinical effects are dose-dependent and range from 2.5-4 hours (Scheep et al. 2012).

The pharmacodynamics of GHB describes at least two distinct binding sites, the GHB- and the GABA_B-receptor. GHB acts as an agonist at the GHB-receptor, which causes an excitatory effect, and as a weak antagonist at the GABA_B-receptor, which causes an inhibitory effect. Activation of both GHB- and GABA_B-receptors is responsible for the addictive properties of GHB. The psychotropic effect involves the release of glutamate, as well as the release and inhibition of release of dopamine. In defined areas of the brain, activation of the GHB-receptor results in the release of glutamate. The dopamine release of GHB is biphasic. Low doses of GHB stimulate dopamine release via the GHB-receptor, higher concentrations then inhibit dopamine release via the GABA_B-receptor, and eventually, after an initial phase of inhibition, dopamine release is again increased via the GHB-receptor. More recently, in addition to the action at the low-affinity metabotropic GABA_B-receptor, a high affinity binding site at the ionotropic $\alpha\beta\delta$ -GABA_A-receptor site has been identified. However, the precise role of this high-affinity binding site still remains elusive (Bay et al. 2014, Vogensen et al. 2013).

The early GHB-withdrawal syndrome resembles the alcohol withdrawal syndrome which is associated with autonomic instability, tremor, anxiety, restlessness, and

insomnia. GHB withdrawal usually lasts 3 to 21 days. However, severe withdrawal syndromes can produce acute delirium and psychosis requiring hospitalization, even leading to intensive care management and fatal outcome (Scheep et al. 2012). The mainstay of management of the GHB-withdrawal syndrome remains the administration of benzodiazepines which primarily act on the GABA_A and high doses are often required (van Noorden et al. 2009). However, more recently, the administration, in particular the titration and tapering of GHB itself has been studied with great success. Only a low level of withdrawal symptoms was experienced, and no patient developed delirium or psychosis (de Jong et al. 2012). Thus, administering GHB could be a superior future approach in the management of GHB-withdrawal. Yet another approach, which at this point has not yet been evaluated, could be the administration of Baclofen, a GABA_B-Agonist in conjunction with benzodiazepines. This approach would cover the psychodynamic properties of GHB and could be equally useful than the administration of GHB. However, this approach has not yet been studied to date.

CASE REPORT

Mr. V. is a 46 year-old French Male, who was found unresponsive in a train from Paris to Zurich. The train police was alerted and at the Emergency Department, he presented with severe disturbance of consciousness, tremor, diaphoresis and muteness. He was afebrile, blood pressure and heart rate were elevated. Laboratory findings revealed an increased creatinine kinase (1057 U/l) and myoglobin (178 mcg/l); electrolytes, renal, thyroid, and liver function tests were normal, as was the cranial CT scan.

Due to the stupor and mutism - meeting DSM-5 criteria for the catatonic specifier (APA 2013) - Mr. V. was managed with repeated doses of lorazepam, 2.5mg every 20 minutes, totaling 7.5mg. Within the hour, his consciousness improved, he was able to interact - though, did not make sense - severely disoriented, cognitively impaired and psychomotor restless. An EEG revealed a medication-induced, increased beta-activity. The urine toxicology tested positive for GHB.

On the floor, a severe hyperactive delirium evolved with disturbances of consciousness, orientation and cognition. The thought process was incoherent, visual hallucinations present: He was sitting in his bed smoking imaginary cigarettes. The mood was irritable, the affect labile and he was agitated. Judgment and insight were severely impaired.

Collateral information revealed that the patient had recently lost his job, suffered from recurrent depression and ordered unknown substances over the internet.

Following the working diagnosis, GHB-dependency, withdrawal, secondary catatonia and subsequent delirium, Mr. V. was administered increasing amounts of lorazepam. Subsequently, after administration of 120mg of Lorazepam, the mental status improved. After stabilization, Mr V. admitted to regular use of GBL and returned to Paris to his family.

DISCUSSION

Mr. V. consumed GBL while being on the train, causing intoxication and subsequent mechanical rhabdomyolysis. In the emergency department he presented with a catatonic stupor which responded to lorazepam administration before developing a severe delirium due to GHB-withdrawal, which in turn was successfully managed with increasing doses of lorazepam.

Catatonia is a syndrome characterized by motor immobility and behavioral abnormalities. To date, catatonic stupor has yet not been reported as a consequence of GHB-withdrawal, however, has been documented in alcohol and abrupt or overly rapid benzodiazepine withdrawal (Geoffroy et al. 2012, Brown & Freeman 2009).

Synaptic transmission and neurotransmitters involved in catatonia include glutamate, GABA and dopamine. The often dramatic response to benzodiazepines in catatonia is a crucial observation supporting the role of GABA-dysfunction in catatonia. In addition, another major theory involves dopamine hypoactivity and glutamate hyperactivity (Dhossche et al. 2010). Thus, it is in itself not surprising that GHB-withdrawal, similar to alcohol- and benzodiazepine-withdrawal, can manifest in a catatonic state.

A number of facts point to the causative role of GHB-withdrawal manifesting as catatonic stupor. For one, the absence of medical illness or other findings explaining the catatonic presentation, next, the rapid response to benzodiazepines, the subsequent withdrawal and delirium clearly indicating GHB-withdrawal, as

well as last, the pathophysiology of catatonia involving a hypo-gabaergic state, which could be caused by regular GHB-use and withdrawal, indicated that in this case, catatonic stupor occurred in the context of GHB-dependence and –withdrawal.

CONCLUSION

In summary, this case illustrates the requirement for a heightened awareness of the growing prevalence of daily GBL- and GHB-use and -dependence, subsequent withdrawal with various presentations including delirium, psychosis and catatonia.

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